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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,003	03/14/2005	Daniel S. Martin	636-C-PCT-US	6708

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EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	**PAPER NUMBER**
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,003	MARTIN ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 26, 2006 (amdt)*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-16,21,46-49 and 54-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-16,21,46-49 and 54-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

No additional claims have been cancelled, claims **2-3, 7-8, 11, 21 and 48-49** have been amended, the disclosure has been amended at page 1, and new claims **54-64** have been added as per the amendment filed April 21, 2006 . No additional supplemental Information Disclosure Statements (IDSs) have been received as of the date of this Office action. The **Fantin et al.** reference submitted by applicant is noted with appreciation. This FAXed copy has been supplemented by a PDF version downloaded from the WEB and the citation has been made of record on the PTO-892 as reference **V**.

Claims **2-16, 21, 46-49 and 54-64** remain in the case.

Claims **2-16, 21 and 46-49** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is very broad because of the exclusive reliance on the generic terms "ATP depleting agents," "pyrimidine-depleting agent," and "an anticancer agent," each of which has <u>not</u> been further defined by any specific chemical structures or structures. In addition the generic term "cancer" covers a vast array of different neoplastic disease conditions with widely varying etiologies and sensitivities to compounds known to have anti-neoplastic activity.

B. The nature of the invention: the invention is directed to a method of causing the death of cancer cells by concomitant administration of three substances which have the effects of i) causing depletion of ATP in cancer cells, ii) causing depletion of pyrimidines from cancer cells, and iii) otherwise attacking the cancer cell life cycle with an anticancer agent, respectively.

C. The state of the prior art in the study of the chemical induction of cell death is not limited to applicant's own work wherein a limited number of chemical substances are shown to be effective in the treatment of a limited number of cancer types. See the PTO-1449 references **#3 and #11** and the PTO-892 references **R, S, T and U**.

D. The level of one of ordinary skill is relatively high, because practice of the instant invention requires an understanding of both medical chemotherapy and associated neoplastic cell biochemistry.

E. The level of predictability in the art is limited by the absence of data to show that the method of inducing neoplastic cell death (necrotic or apoptotic) applies to more than a limited number of neoplastic disease conditions. The various Martin et al. references disclose the effects of several different anti-cancer drugs on mouse breast tumors only. The Geschwind et al. group (PTO-1449 ref. **#3**) has disclosed the efficacy of 3-bromopyruvate against rabbit liver cancer, but this was observed to occur without the presence of the "PMA" combination used by Martin et al. Therefore, the data presently in hand fails to permit the ordinary practitioner to extrapolate to "cancer" in general.

F. The amount of direction provided by the inventor in detail with regard to a limited number of soft tissue neoplastic diseases. However, applicant does not describe how to treat any one of the various pancreatic cancers, liver cancers, bone cancers or brain cancers.

G. The existence of working examples is limited to breast cancer, sarcomas, leukemia and transplanted breast cancers.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be undue because applicant has not limited the instant claims to the specific groups of active ingredients or to the specific neoplastic disease conditions enabled by the disclosure.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant's amendments to the noted claims have not effectively addressed this rejection. Applicant may elect to add new test data by declaration in order to properly enable the subject.

matter presently not enabled herein. Examiner notes with appreciation the newly added claims wherein the instant issue is not a problem. .

Claims **2-16, 21 and 46-49** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention; the scope is excessive in view of the disclosed exemplifications.

The functional definitions of the components of the pharmaceutically active composition in claims **2, 21 and 46** are directed to a vast number of chemical compounds which have not been described in the instant disclosure in a manner permitting the ordinary practitioner to have the guidance necessary to make or to use a very large proportion of the compound mixtures encompassed by said definitions. Examiner finds at page 38 of the disclosure only 4 combinations of ATP-depleting and other compounds provided in the "Examples" section and none of these compound mixtures defines the subject matter in sufficient detail to permit allowance of claims wherein the individual components of said mixtures are defined generically. Examiner suggests that each of the instant exemplifications be made the basis of a separate claim or set of claims with limitation to the specific neoplastic disease condition(s) enabled by specific embodiments. The generic term "cancer" is also not appropriate in the instant patent claims because the medical treatment of neoplastic disease conditions remains highly unpredictable, particularly in light of the very small number of specific exemplifications of neoplastic disease treatments disclosed herein (applicant has disclosed tests of the instant claimed method on human breast cancer xenografts at pages 23, 29, 39, and 41; a human ovarian cancer xenograft at page 39; and a human pancreatic cancer xenograft at page 39).

Examiner also reminds applicant that *Brenner v. Manson* remains good law (148 USPQ 689 (S. Ct., 1966) at p. 696, column 1) and stands for the proposition that "[A] patent is not a hunting license ... [i]t is not a reward for the search, but compensation for its successful completion."

Examiner expects that applicant may elect to file multiple applications over time as research on the actual scope of the instant claimed invention is being conducted as an ongoing effort, with additional data being added to each application as said data becomes available

either directly during drafting or subsequently as a declaration. The accumulation of additional data is critical to establishing the actual scope of the instant invention as envisioned, a topic of repeated, but incompletely enabled, speculation within the instant disclosure. And without said additional enabling experimental data, allowance of claims of greater scope than that suggested above is unlikely.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant's amendments to the noted claims have not effectively addressed this rejection.

Claims **8, 54 and 56-64** is objected to because of the following informalities:

In claim **8** at line 4, the term "Aminonicotinamide" is improperly capitalized. See also claim **54** at line 6, claim **58** ("Bromopyruvate" should be --bromopyruvate --) for the same or a similar error.

In claims **56 and 57** the term "Composition" is improperly capitalized.

In claims **59 and 60** the term "Adria" apparently refers to an active ingredient but the remainder of the claim fails to define the term in a manner permitting the ordinary practitioner to know the chemical identity of the active ingredient. Is applicant using an abbreviation to refer to "Adriamycin," the hydrochloride salt of doxorubicin? A clarifying amendment is respectfully requested.

In claims **61 and 62** the term "F16" is a trademark and therefore inappropriate as the sole identifying term for a chemical substance because the owner of the trademark can change the definition of the trademark at any tome. Examiner has added a "Product Information sheet" from Caymen Chemicals (PTO-892 ref. **W**) wherein the name of the substance is provided. Examiner suggests replacement of the noted term with -- 4[(1E)-2-(1H-indol-3-yl)ethenyl]-1-methyl-pyridinium iodide (F16) --.

In claims **63 and 64** at line 3, the term "the cancer or breast" includes a grammatical error. Did applicant intend the term to read
-- the cancer is breast --?

Appropriate correction is required.

Claims **2-16, 21, 46-49 and 54-64** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim **2** at lines 2-5, the term "at concentrations which deplete the ATP levels to at least 15% of normal in cancer cells" is a method of treating limitation and therefore not properly part of a composition claim. Deletion is respectfully requested. Alternatively the noted term may be replaced by the term -- effective amount -- or the like.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant's amendments to the noted claims have not effectively addressed this rejection. Therefore, the rejection has been maintained. Applicant is referred to comments below in re this same issue in other composition claims.

Claim **2** is incomplete because the functional terms at lines 5-7 beginning with the term "mitochondrial" are not further defined as actual chemical species. The noted terms also lack adequately defined metes and bounds and, because of their functional nature said terms are improperly prospective because they read on species not presently known to have the described effects. See also claims **3, 21, 46 and 46** for the same errors. See claim **4** for a similar error involving the functional terms "pyrimidine-depleting agent" and "pyrimidine antagonist."

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Functional language is not acceptable for claims defining active ingredients in a pharmaceutical composition claim. Applicant is asking the ordinary practitioner to guess what compounds other than those specifically disclosed have the functional property. This situation is similar to the issue decided in *Ex parte Balzarini et al.* 21, USPQ 2d 1892, 1894 (BPAI, 1991): applicant is in effect asking the examiner to believe that claims directed to medicinal treatments of diseases in highly unpredictable art areas are proper in the absence of sufficient

test data in support of the efficacy of the alleged treating agent(s) and the chemical identity or identities of said agent(s).

In claims **2, 3, 21, 46, 48 and 49** the terms "cancer," "ATP depleting agents," and "pyrimidine-depleting agent" are each lacking adequately defined metes and bounds because there is no claim listed which defines the particular diseases being referred to by the first generic term, or to the particular chemical identities of the medicinally active compounds encompassed by the last three generic terms.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant's amendments to the noted claims have not effectively addressed this rejection. Therefore, the rejection has been maintained in part. However, Examiner does note that some of the newly added claims avoid these grounds of rejection.

In claim **3** at line 2, the term "substantially better effect" is indefinite because it is unclear from the remainder of the claim how the metes and bounds of said claim is distinguished from claim **2**. It appears that claim **3** is only a recapitulation of claim **2** in a manner intended to emphasize an effect inherent in claim **2**, and therefore that claim **3** fails to further limit the scope of claim **2** (improperly dependence). Also, the particular "effect" is assumed by examiner to be a medicinal effect, but is not further defined. The absent definition renders the instant claim incomplete. See also claims **21 and 49** for the same error.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

The noted term ("substantially better effect") is a method of treatment limitation and therefore has no patentable weight in a composition claim. Deletion is respectfully requested.

Claim **8** is inconsistent with the content of claim **2**. Applicant is referred to the last two lines of claim **2** and line 2 of claim **8**: the former claim excludes "MMPR" by proviso and the latter claim specifically includes "MMPR," suggesting a lack of proper antecedent basis. Clarification is respectfully requested.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant's amendment's to claims **2 and 3** making more explicit the exclusion of MMPR does not effectively address this problem; i.e. if claim **2** excludes MMPR, then claim **8** cannot add it back.

Claim **8** recites the limitation of individual "ATP-depleting agents" in reference to the requirement of "a combination of ATP-depleting agents" in claim **2**. There is insufficient antecedent basis for the limitation in claim **8** in the noted limitation found in the proviso now at the end of parent claim **2** (and in claim **3**). See also claims **9-11** for the same error. See also claims **12-16** for a very similar error.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

The newly amended claim **2** has the effect of excluding applicant's previously disclosed, MMPR-containing, compositions as prior art, but also point out that applicant has not provided enablng support for the vast number of remaining alternatives encompassed by the relentlessly functional language of claim **2**. In addition, the proviso makes dependent claims **8** wherein MMPR is cited as an active ingredient lacking in proper antecedent basis.

In claims **54 and 55** the term "composition" is incomplete because the subject matter clearly indicates that applicant intends to apply a mixture of substances to the treatment of a disease. If this is applicant's intention, examiner suggests that the claims should be restyled as a --pharmaceutical composition -- claim. The standard format for -- pharmaceutical composition -- claims is as follows: -- A pharmaceutical composition comprising {active ingredient(s)} in combination with a pharmaceutically acceptable carrier.--

Applicant's arguments with respect to claims **2-3, 5-9, 21 and 46-49** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by the introduction of new claims.

In claims **54 and 55** at line 2, the term "at concentration" is technically incorrect in the medical context. Did applicant intend the term to read -- to be administered at dosages --.

Applicant's arguments with respect to claims **2-3, 5-9, 21 and 46-49** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by the introduction of new claims.

In claims **54 and 55** the term "comprises" is incorrect because this term in correctly implies that the mixture of active ingredients needs to be supplemented by one or more additional active ingredients. Said term is also superfluous because the previous term "comprising" at line 1 is sufficient to protect applicant's interest against an infringer who may claim the noted active ingredients in combination with one or more other active ingredients. Examiner suggests replacing the term "comprising" with the term -- is --. See also claims **56-62** wherein the term "wherein the combination further comprises" should be replaced with the term -- further comprising -- in order for these claims to be properly dependent from amended claims **54 and 55**.

Applicant's arguments with respect to claims **2-3, 5-9, 21 and 46-49** have been considered but are moot in view of the new grounds of rejection. This new ground of rejection was necessitated by the introduction of new claims.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **21, 46-49 and 63-64** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***68-77*** of copending Application No. **10/172,346**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the specified active ingredients of the claimed compositions are directed to substantially overlapping subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant has acknowledged the possible need for a Terminal Disclaimer but has presently not made one of record. Therefore the instant rejection has been maintained.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims **2-3, 5-9, 11, 16, 21, 54-55 and 59-60** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Nord et al.** (PTO-1449 ref. **#11**).

Applicant is referred to page 380, Table 3 (explanation at the top of the table) and associated explanatory text.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant is referred to **Nord et al.** at p. 383, column 1, last sentence of the last paragraph wherein applicant admits that MMPR is the most effective compound for inhibition of ATP in cancer cells but that this compound cannot be administered by itself because the

compound "is not sufficiently active to induce [tumor regression] ... at host-tolerant doses" and that the combination of MMPR, PALA and AN produces the optimal tumor regression.

Applicant is requested to note that the instant "composition claims" are anticipated by the instant disclosure because the limitation of "15% or less ATP levels in a treated cancer cell" is not a proper limitation for a composition claim; i.e. this limitation has no patentable weight in a composition claim. Therefore, for those claims wherein MMPR has been excluded, this reference (at p. 383) also discloses in the noted sentence that PALA and AN are also effective suppressors of the ATP level in cancer cells and can be present in an effective composition of the kind claimed, thereby anticipating the claimed subject matter whether MMPR is excluded or not.

It is examiner considered view, in light of the extensive prior art available, that the instant disclosure and the companion '346 application will only support method of treatment claims of the kind found allowable in the '346 application.

Claims **2-3, 5-9, 11, 16, 21, 54-55 and 59-60** are rejected under 35 U.S.C. §102(**b**) as being anticipated by **Stolfi et al.** (PTO-1449 ref. **R**).

Applicant is referred to the fourth paragraph of column 1 at page 4075 and the preceding two paragraphs.

Applicant's arguments filed April 21, 2006 have been fully considered but they are not persuasive.

Applicant is referred to the response following the first art rejection as being fully responsive to applicant's arguments in re this rejection.

For equivalent references see **Colifiori et al.** (PTO-892 ref. **S**) at page 1943, paragraph bridging columns 1 and 2; **Martin et al.** (PTO-892 ref. **T**) in the paragraph bridging pages 656 and 657; and **Koutcher et al.** (PTO-892 ref. **U**) at page 1145, last two paragraphs of the abstract.

Applicant is referred to the response following the first art rejection as being fully responsive to applicant's arguments in re these rejections.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 571,273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. S. Anna Jiang, can be reached at **571-272-0627**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
03/27/2007

3/27/07

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